18. (New) The method of claim 16 wherein the first and second group members are administered in association with each other.

B3 cont'd

19. (New) The method of claim 1, wherein the need for surgery to treat said pathological condition is avoided, delayed or reduced by administering the first group member.

20. (New) The method of claim 1, wherein the first group member is administered in association with a treatment to avoid, delay or reduce the need for surgery to treat said pathological condition.

21. (New) The method of claim 11 wherein the first group member is administered in association with a treatment to relieve symptomatic discomfort.

22. (New) The method of claim 11, wherein the need for surgery to treat said pathological condition is avoided, delayed or reduced by administering the first group member.

23. (New) The method of claim 11, wherein the first group member is administered in association with a treatment to avoid, delay or reduce the need for surgery to treat said pathological condition.

REMARKS

Status of the Claims

Pending claims 1-14 were rejected provisionally under the judicially-created doctrine of obviousness-type double patenting over claims 1-10 of co-pending Application No. 09/663528. Claims 1, 2, 4, 11, 12 and 14 were rejected under 35 U.S.C. §102(b) as being anticipated by Martel-Pelletier et al. Claims 3, 5-10 and 13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Martel-Pelletier et al. in view of Marcolongo et al. and a statement from page 1 of Applicants' specification. Claim 3, as amended by Applicants' March 9, 2001 Preliminary Amendment, was rejected for not complying with the written description

requirement of 35 U.S.C. §112, ¶1. The related Preliminary Amendment to the specification was objected to as new matter under 35 U.S.C. §132. Applicants traverse the rejections and objection.

The Amendment

The specification has been amended to correct an obvious typographical error. No new matter has been presented since the application clearly relates to tumor necrosis factor, not tissue.

Claims 1 and 11 have been amended and new claims 15-23 have been added. Support for amendments to claims 1 and 11 can be found at least at p. 3, ln. 14 to p. 4, ln. 4; p. 6, lns. 1-6 and 14-18; and p. 7, lns. 7-9 of the application, which makes clear that Applicants' invention is directed to methods of treating an underlying biochemical or physiological cause of a claimed pathological condition and not just to the amelioration of symptoms associated with the pathological condition. The claims have also been amended to standardize the use of the singular "condition," since the articles "a" and "an" are used throughout the claims to mean one or more.

Support for new claims 15-23 can be found in numerous locations throughout the application, both explicitly and inherently through the teachings contained therein; for example, p. 2, lns. 14-15 (IL-1 receptors), p. 6, ln. 19 to p. 7, ln. 6 (reduction of IL-1 and TNF-α synthesis) and p. 6, lns. 1-3 (treatment of symptoms). Consequently, no new matter has been added by the amendment.

§112, ¶1 Rejection of Claim 3 and
§132 Objection to Related Amendment to Disclosure

The Office Action rejected claim 3 under §112, ¶1, stating that the claim term "pulmonary fibrosis" was not specifically described in the specification. The Office Action also

objected to the amendment adding "pulmonary fibrosis" to the specification as new matter under §132. Because the test for compliance with §112's written description requirement and for §132 new matter issues is essentially the same, Applicants will treat this rejection/objection as a single issue below. See *Manual of Patent Examining and Procedure*, § 2163.01.

Specific disclosure of "pulmonary fibrosis" in the specification as filed is not a requirement of the law of written description. See *In re Edwards*, 568 F.2d 1349, 1351-52, 196 U.S.P.Q. 465, 467 (C.C.P.A. 1978). All that the law requires is that "pulmonary fibrosis" be among those diseases suggested by the general language in the application to one of ordinary skill in the art. See *Forssmann v. Matsuo*, 23 U.S.P.Q.2d 1548, 1550 (Bd. Pat. App. Int. 1992). A description of the genus of diseases covered by Applicants' claimed invention is sufficient to support the claimed species of "pulmonary fibrosis" if the description contains "blaze marks" directing the skilled artisan to the species. See *In re Ruschig*, 379 F.2d 990, 994-95, 154 U.S.P.Q. 118, 122 (C.C.P.A. 1967); *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1326-27, 56 U.S.P.Q.2d 1481, 1486 (Fed. Cir. 2000).

In the March 9, 2001 Preliminary Amendment, Applicants pointed to the so-called blaze marks in the application that lead one of skill in the art to include pulmonary fibrosis among the genus of claimed diseases. The skilled artisan would know that pulmonary fibrosis is an inflammatory disease of the lungs encompassed within the genus of inflammatory and autoimmune diseases described in the Application. Applicants made reference to Steadman's Medical Dictionary (26th Edition) for such a definition of pulmonary fibrosis: "an acute to chronic inflammatory process of the lungs . . . either completely ideopathic or associated with collagen-vascular disease." (See Exhibit B.) Applicants then directed the Examiner to at least four places in the application where inflammatory diseases were referenced broadly.

It was then incumbent on the Examiner to present evidence or reasoning why the skilled artisan would not understand that pulmonary fibrosis fell within Applicants' claimed genus of diseases. See *Manual of Patent Examining Procedure*, § 2163.04.

Applicants again respectfully direct the Examiner to portions of the application supporting the species of pulmonary fibrosis. The specification throughout states that "the pathological conditions contemplated herein ... broadly encompass the inflammatory and autoimmune diseases" (p. 1, lns. 18-19), "the use of diacerein and rhein in the treatment of inflammatory and autoimmune diseases" (p. 4, ln. 7), "method of treatment including the administration of diacerein or rhein to patients suffering from the inflammatory and auto immune diseases" (p. 6, ln. 14-16), Claim 2, etc. Attention is also called to p. 5, lns. 17-18, wherein it is noted that "IL-1 and TNF... contribute to the fibrosis and tissue degeneration of the chronic proliferative phase of inflammation" (emphasis supplied), as well as to many other instances wherein an inflammatory condition is referenced broadly as amenable to treatment as described and claimed.

Applicants now also provide further evidence that pulmonary fibrosis is supported by the application as filed. One of ordinary skill in the art would have known that pulmonary fibrosis is an inflammatory disease of the lungs characterized by increased IL-1 and TNF-α levels, as the abstracts of the publications by Martinet et al. and Zhang et al. clearly indicate. (See Exhibits C and D.) This blaze mark for the disease – and for the genus of diseases claimed by Applicants – is disclosed for instance in the application at p. 1, lns. 10-11 ("The invention specifically resides in a method for treatment of pathological conditions characterized by an increased IL-1 and/or TNF-α level..."), p. 6, lns. 14-17 ("An objective of the invention was to provide a method of treatment [for] patients suffering from the inflammatory and autoimmune

diseases, in which inflammatory cytokines, such as interleukin-1 (IL-1) and tissue necrosis factor α (TNF-α) are present to an increased degree..."), claim 1 as originally filed ("Method of treating pathological conditions characterized by an increased IL-1 and/or TNF-α level...") and claim 11 as originally filed ("Method of treating inflammatory and autoimmune conditions characterized by an increased IL-1 and/or TNF-α level...").

Consequently, Applicants respectfully submit that the written description rejection of claim 3 (and related objection to amendments to the specification) has been traversed, and request that the rejection be withdrawn.

The Provisional Rejection of Claims 1-14
For Obviousness-Type Double Patenting

The Office Action provisionally rejected claims 1-14 under the judicially-created doctrine of obviousness-type double patenting over claims 1-10 of co-pending Application No. 09/663528. The Office Action, although admitting that the claims are not identical, alleges that they are not patentably distinct from each other because end stage osteoarthritis is an inflammatory disease. Applicants respectfully traverse this rejection.

Under the judicially-created doctrine of obviousness-type double patenting, the law is clear that "[i]t is the *claims*, not the specification, that define an invention. And it is the *claims* that are compared when assessing double patenting." *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 943, 22 U.S.P.Q.2d 1119, 1125 (Fed. Cir. 1992) (citations omitted; emphasis added). Applicants submit that when the claims of the Appl. No. 09/663528 are compared to the claimed invention of the present application, it is apparent that the asserted claims cannot, without more, lead one to the invention of the instant application.

Only by reference to the teachings of the specification of Appl. No. 09/663528 could an argument be made that the total disclosure could lead to the present invention.

However, under the law, this is not adequate to establish obviousness-type double patenting. See *Manual of Patent Examining Procedure*, § 804. Therefore, Applicants submit that the obviousness-type double patenting rejection is inappropriate, and requests that it be withdrawn.

Rejections Under §102(b)

The Office Action rejected claims 1, 2, 4, 11, 12 and 14 as anticipated by Martel-Pelletier et al., a paper co-authored by one of the instant inventors and sponsored by the Assignee. According to the rejection, this reference discloses a method of treating a subject having osteoarthritis ("OA") with diacerein and rhein. Applicants respectfully disagree.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). The claims rejected under §102(b) contain the elements of, inter alia, a *method of treating* the specified pathological conditions *comprising administering to a subject* a *therapeutically effective amount* of diacerein and/or rhein. Applicants respectfully submit that the teachings of Martel-Pelletier et al. do not contain the above-emphasized elements.

Martel-Pelletier et al. discloses the *in vitro* testing of diacerein and rhein on cultured cartilage tissue. Nowhere in the reference is there disclosed a method of treating a subject having OA, the administration of diacerein or rhein to subjects suffering from OA – or from any disease – or what a therapeutically effective amount of diacerein or rhein would be, *in vivo*, when administered to a human patient. Indeed, Martel-Pelletier does not establish that the administration of diacerein or rhein will treat the underlying cause of a condition as claimed in a

subject. The absence of these elements from Martel-Pelletier et al. requires that this §102(b) rejection be withdrawn.

Rejections Under §103(a)

The Office Action rejected claims 3, 5-10 and 13 as obvious over Martel-Pelletier et al. in view of Marcolongo et al. and Applicants' admissions on page 1 of the application. Applicants respectfully traverse this rejection.

For the reasons set out above concerning the teachings of Martel-Pelletier et al., the rejection is independently traversed. Beyond this, the rejection is traversed because Applicants' invention is nonobvious in light of the cited art. Applicants' inventive contribution primarily resides in the treatment of an *underlying pathological cause* of any of the claimed genus of diseases and is not just limited to the alleviation of symptoms. Martel-Pelletier et al. discloses nothing more than the use of diacerein and rhein to inhibit the *in vitro* synthesis of IL-1 in cultured cartilage tissue. The authors draw no conclusion that diacerein or rhein will stop an underlying cause of OA – *i.e.*, the destruction of cartilage tissue – when administered to humans. In fact, the authors state at p.760 that "Diacerhein is currently under investigation *in vivo* in patients with hip and knee OA *to explore its potential* structure modifying effects. The latter should yield useful information regarding the clinical relevance of this *in vitro* study." (Emphasis added.) Without such data and a reduction to practice – that is the knowledge that diacerein and rhein are relevant to treating humans – the reference cannot enable an anticipating disclosure; as the Martel-Pelletier authors note, it requires human data to know the relevance of the paper.

The Marcolongo et al. reference adds little more than Martel-Pelletier et al. It does not teach the inventive contribution of the instant application: that diacerein and/or rhein can treat an *underlying cause* of a pathological condition characterized by increased IL-1 and/or

TNF-α levels. At most, Marcolongo et al. teaches that a 100 mg dose of diacerein given daily for two months can reduce the *symptoms* of OA (pain, tenderness, etc.). There is no suggestion that this dose – or any dose – will stop or delay cartilage destruction in these patients. Furthermore, Marcolongo et al. does not even mention IL-1 or TNF-α levels or their production, let alone reduction in their synthesis in patients after treatment with diacerein.

Applicants' cited "admissions" from page 1 of the application do not fill in the gaps in the teachings of the cited art. Applicants admit no more than that the diseases listed on page 1, lns. 10-14 are associated with increased IL-1 and/or TNF-α levels. There is no admission in the application that the prior art teaches a proper dosage of diacerein or rhein that can treat the underlying pathological causes of the enumerated diseases. The mere existence of an association between increased IL-1 and/or TNF-α levels and an enumerated disease would not teach one of ordinary skill in the art that an inhibitor of IL-1 and/or TNF-α will have an effect on an underlying pathological cause of the disease.

of course it does!

Therefore, Applicants respectfully submit that the rejection is inappropriate, and request that it be withdrawn.

NOTICE OF CONTACT CHANGE

Applicants respectfully direct the Examiner to the undersigned for any telephone contact. The mailing address remains "IP Docketing" at the below-listed firm and address.

CONCLUSION

Applicants submit that the instant Amendment and Remarks are sufficient to overcome the outstanding rejections of the claims. Consequently, Applicants submit that the claims are now in a condition for allowance and respectfully request that they be allowed to go to issuance.

Respectfully submitted,

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